PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg
Certificate

REGISTRERINGSVERKET • PATENT

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) *Sökande* *AstraZeneca AB, Södertälje SE*
Applicant (s)

(21) *Patentansökningsnummer* *0201110-4*
Patent application number

(86) *Ingivningsdatum* *2002-04-12*
Date of filing

Stockholm, 2003-03-18

För Patent- och registreringsverket
For the Patent- and Registration Office

Christina Vängborg

Avgift
Fee *170:-*

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

NEW FILM COATING

Field of the invention

The present invention relates to a new film coating. More specifically the present invention relates to a new film coating for the achievement of controlled release from pharmaceutical formulations such as tablets, pellets, etc., wherein the film coating may be applied in a substantially aqueous environment. Furthermore, the invention provides a process for the preparation of such a film coating.

Background of the invention

Oral administration of a drug is the most convenient for the patient. Proper formulations must also meet the requirements of safety and simplicity. Depending on the properties of a drug and the therapeutic requirements, the drug is formulated differently so that the drug has the desired release profile.

For many active substances or drugs it is desirable that the formulation results in the controlled release of the active substance or drug. An example of such an active substance is metoprolol. In principle two main types of controlled-release formulation dosage forms exist; the matrix system where the drug is mixed with the matrix material (often a polymer or a wax); and the drug reservoir system where the drug is formulated into a core (tablet or pellets) surrounded by a polymeric film. The film is then a release rate-controlling barrier determined by, e.g., its dissolution rate, its permeability, the solubility of the substance, etc.

A popular controlled-release formulation includes film coating a drug which is in small discrete units. By formulating the drug into discrete units covered by a film coating, the formulation has several interesting features, e.g., flexibility in dosage and modification of release properties, different dosage forms can be developed, dose size is adaptable to suit fixed combinations, tablets can be made divisible, etc. In a number of studies it was shown that safe, simple, and convenient therapy could be achieved utilising this principle for the

drug metoprolol and its salts (Ragnarsson et al, *Drug Develop Ind Pharmacy* 13, 1495 (1987); Sandberg et al, *Eur J Clin Pharmacol* 33, S3 (1988) and S9 (1988); Ragnarsson et al, *Int J Pharmaceutics* 79, 223 (1992); Sandberg et al, *Ibid* 68, 167 (1991); Sandberg et al, *Pharmaceutical Res* 10, 28 (1993); Sandberg et al, *Drug Invest* 6, 320 (1993); Sandberg, *Thesis* Uppsala University, 1994).

The formulation of metoprolol into pellets according to the above mentioned references utilised a film coating sprayed from a solution of ethyl cellulose and hydroxypropyl methyl cellulose in an organic solvent. However, for environmental reasons it will be necessary in the near future to utilise water based film forming systems for this and other drugs to be formulated as pellet systems. Also, tablet coatings in general utilising organic solvents must for the same reasons be exchanged with water based film forming materials. Thus, much effort has been directed to find suitable water based systems for film coatings in drug delivery systems.

Water based film-forming polymer latexes for the pharmaceutical industry have been known since the early eighties when commercial dispersions more frequently appeared on the market (e.g., Aquacoat, FMC Corp.; Eudragit E-30D, Röhm Pharma). Further development has given several other products that have been tested and reported in a number of publications (Petereit and Weisbrod, *Eur J Pharmaceutics and Biopharm* 47, 15 (1999); Petereit et al, *Ibid*, 41, 219 (1995); Amighi and Moës, *STP Pharma Sci* 7, 141 (1997); Bodmeier and Paeratukul, *Pharm Res* 11, 882 (1994); Ozturk et al, *J Controlled Release* 14, 203 (1990).Goodhart et al, *Pharmaceutical Tech* April, 64 (1984); Bodmeier and Paeratakul *Int J Pharmceutics* 152, 17 (1997); Bodmeier and Paeratakul *Drug Develop Ind Pharmacy* 20, 1517 (1994)).

A problem with water based film-forming polymers is that to obtain good properties for the film coating anti-sticking agents need to be added. Anti-sticking agents, also named detackifiers, glidants, and lubricants, are well-known agents and can often result in the film coating not being easy to work with. Commonly used anti-sticking agents include glyceryl

monostearate (GMS), talc, and silica. However, often these agents must first be dispersed with other added materials, preferably surfactants or amphiphilic polymers, to obtain more homogeneous systems.

A popular film coating dispersion is Eudragit® NE30D (Röhm). Eudragit® NE30D has a low Tg and contains approximately 28.5 % w/w particles of the copolymer poly(ethylacrylate - co-methylmethacrylate), and approximately 1.5 %w/w of the non-ionic tenside Nonoxynol 100 (a polyoxyethylated nonylphenol) as the stabiliser. However, to obtain best spraying conditions and technical appearance of the film-coated pellets, the anti-sticking agent GMS has to be added to the dispersion as reported by Petereit *et al.* 1995 (*supra*) and Petereit and Weisbrod, (1999) (*supra*). However, for best performance of the dispersion during spraying the GMS was dispersed with an extra surface active agent, e.g., polysorbate 80 (PS80). On the other hand, we have found that it has been difficult to obtain results with acceptable reproducibility with respect to, e.g., permeability and release rates from formulations manufactured according to these suggested procedures. One tentative explanation for this might be that the properties of the GMS/PS80 dispersion, e.g., size of dispersed particles, highly depend on process parameters like temperature, type of mixing etc, which also can be concluded from the results by Petereit *et al.* 1995 (*supra*) and Petereit and Weisbrod, (1999) (*supra*)

The addition of anti-sticking agents, and the addition of surface active molecules, talc or stearates with Eudragits for the controlled release of different types of drugs has been reported by a large number of groups including Wolff et al; WO 00/13687; Wolff et al, WO 00/13686; Nagy et al, WO 99/42087; Lee et al, WO 99/30685; Eichel et al, US 5,529,790; Eichel US 5,478,573; Chen, US 5,260,068; Petereit et al, EP 403,959.

Examples of other dispersions known in the field are Kollicoat® SR30D (BASF), Eudragit® RL30D (Röhm) and Eudragit® RS30D (Röhm). However, due to their high Tg these polymer dispersions form brittle films and need therefore a plasticizer such as triacetin, triethyl citrate (TEC) or acetyl triethyl citrate (ATEC) in order to be useful for

coating application and film formation (Kolter, K et al., *Proc. Int. Symp. Controlled Release Bioact. Mater.*, 27, 425, 2000; G Cole (Ed) *Pharmaceutical Coating Technology*, Taylor and Francis Ltd 1995). However, the use of the plasticizer in a film coating can have a destabilizing effect on the film, probably caused by the migration of small molecules, which can result in the film coating exhibiting changes in its properties with time (see e.g., Gutiérrez Rocca, *PhD Thesis* The University of Texas at Austin, 1993). Also, the presence of stabilizers of the latex particles in a dispersion creates similar problems as, e.g., added plasticizers; i.e., migration of the stabilizers in the film, which can result in the film coating exhibiting changes in its properties with time.

Thus, available latex polymers when used as coating materials present three major problems: (a) sticky pellets may result, due to a low Tg, which then would need extra antisticking agent,s or other additives\excipients, (b) brittle pellets may result, due to a high Tg, which then would need extra plasticizer or other additives\excipients, and (c) migration of additives\excipients, e.g., stabilizers in the film, which then might exhibit changes in properties with time.

Purpose of the invention

The purpose of the present invention is to provide a new film coating system that does not have the above mentioned problems. Improved properties of the new film coating system are, for example, no need for extra additives\excipients to the dispersion before the film forming process, non-stickiness and reproducibility during processing. Another aspect of the invention is to provide a method for synthesising the polymer dispersions as well as manufacturing them into coated formulations, for example pellets or tablets, utilising this new film forming system.

Summary of the invention

The invention is based on a novel polymer. The applicants have found that the polymer can be used as a water based film-forming polymer. The film coating can serve as a barrier giving close to constant release (zero-order) from the formulation. In addition, the

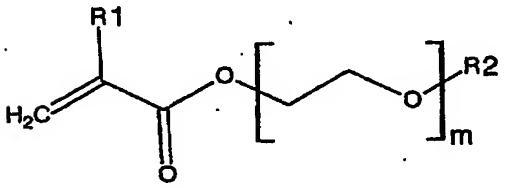
physical properties of the film produced are such that minimal processing problems, such as adhesion, are experienced. Moreover, the films can be reproducibly produced with these improved properties.

The polymer of the invention comprises a polymer between the following monomers:

ethyl acrylate;

methyl methacrylate; and

a monomer characterized by formula I:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

R2 is hydrogen or a carbon chain having 1 to 20 carbon atoms.

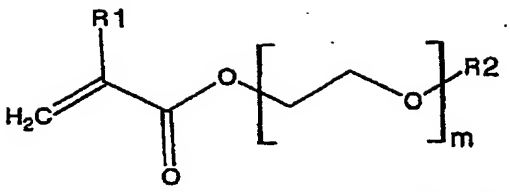
The polymer can be used in a composition. Optionally, the composition can include one or more pharmaceutically acceptable additives\excipients.

In another aspect of the invention, the invention provides a film coating for use in coating pharmaceutical formulations comprising a dispersion which comprises a polymer between:

ethyl acrylate;

methyl methacrylate; and

a monomer characterized by formula I:



(I)

wherein m is an integer from 1-30, R1 is hydrogen or methyl, and R2 is hydrogen or a carbon chain having 1 to 20 carbon atoms.

Preferred values of the substituents R1 and R2 and the integer m will now be given. It will be understood that these values may be used in embodiments described hereinbefore and hereinafter. In a preferred embodiment, R1 is hydrogen or methyl. For example, R1 is hydrogen. For example, R1 is methyl. In a preferred embodiment R2 has 11 to 18 carbon atoms, e.g., 12, 13, 14, 15, 16, or 17 carbon atoms. For example, R2 has 11 carbon atoms. For example, R2 has 12 carbon atoms. For example, R2 has 13 carbon atoms. For example, R2 has 14 carbon atoms. For example, R2 has 15 carbon atoms. For example, R2 has 16 carbon atoms. For example, R2 has 17 carbon atoms. For example, R2 has 18 carbon atoms. In a preferred embodiment the integer m is preferably from 1 to 25, e.g., m is an integer from 1 to 4, e.g., 1, 2, 3 or 4. In another embodiment, m is an integer from 10 to 25, for example, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25.

In one embodiment, the monomer is defined as m is 4, R1 is hydrogen and R2 has 13 carbon atoms. In another embodiment, the monomer is defined as m is 10, R1 is hydrogen and R2 has 11 carbon atoms. In yet another embodiment, the monomer is defined as m is 25, R1 is hydrogen and R2 has 18 carbon atoms. These monomers are also known as alkyl polyethoxy acrylate monomers.

In still yet another embodiment, the monomer is defined as m is 1, R1 is methyl and R2 is hydrogen. This monomer is also known as a hydroxyethyl methacrylate.

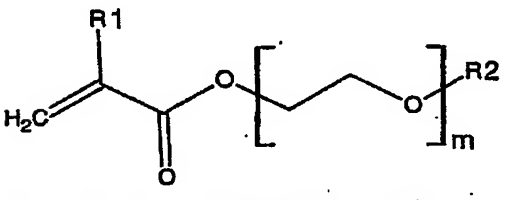
Optionally, the film coating can include one or more pharmaceutically acceptable additives\excipients. The film coat is deposited from a water-containing liquid.

In yet another aspect, the invention provides a film coat covering a pharmaceutical core wherein the core comprises a pharmacologically active ingredient and the film coat comprises a polymer of:

ethyl acrylate;

methyl methacrylate; and

a monomer characterized by formula I:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

R2 is hydrogen or a carbon chain having 1 to 20 carbon atoms.

In one embodiment, the monomer is defined as m is 4, R1 is hydrogen and R2 has 13 carbon atoms. In another embodiment, the monomer is defined as m is 10, R1 is hydrogen and R2 has 11 carbon atoms. In yet another embodiment, the monomer is defined as m is 25, R1 is hydrogen and R2 has 18 carbon atoms. In still yet another embodiment, the monomer is defined as m is 1, R1 is methyl and R2 is hydrogen.

Optionally, the film coating can include one or more pharmaceutically acceptable additives\excipients. The film coat is deposited from a water-containing liquid.

The pharmacologically active ingredient can be any active ingredient. In one embodiment, the active ingredient is a beta-blocking adrenergic agent such as metoprolol or a

pharmaceutically acceptable salt thereof. The metoprolol salt can be a tartrate, succinate, fumarate or benzoate salt.

In another aspect of the invention, the invention provides a pharmaceutical formulation including:

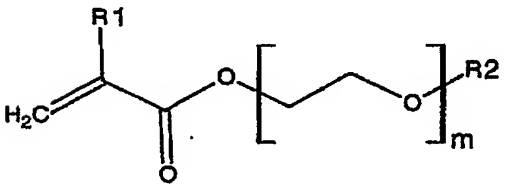
a) a pharmaceutical core comprising a pharmacologically active ingredient; and

b) a film coat comprising a polymer of the following monomers:

(i) ethyl acrylate;

(ii) methyl methacrylate; and,

(iii) a monomer of formula I:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

R2 is a carbon chain having 1 to 20 carbon atoms or is hydrogen.

In one embodiment, the monomer is defined as m is 4, R1 is hydrogen and R2 has 13 carbon atoms. In another embodiment, the monomer is defined as m is 10, R1 is hydrogen and R2 has 11 carbon atoms. In yet another embodiment, the monomer is defined as m is 25, R1 is hydrogen and R2 has 18 carbon atoms. In still yet another embodiment, the monomer is defined as m is 1, R1 is methyl and R2 is hydrogen. Optionally, the film coating can include one or more pharmaceutically acceptable additives\excipients. The film coat is deposited from a water-containing liquid.

The invention also provides a pharmaceutical formulation including a pharmacologically active ingredient which is provided in a plurality of beads wherein each of the beads is coated with a film coat as described herein. In one embodiment, the formulation can be a

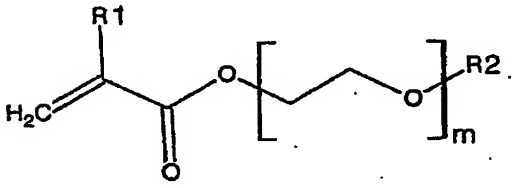
controlled-release formulation. The pharmacologically active ingredient is preferably an ingredient that has activity in the treatment of cardiovascular or gastrointestinal diseases. In one embodiment, the pharmacologically active ingredient is a beta-blocking adrenergic agent such as metoprolol or a pharmaceutically acceptable salt thereof. The metoprolol salt is a tartrate, succinate, fumarate or benzoate salt .

The invention further comprises a process for the preparation of a polymer comprising polymerising:

ethyl acrylate;

methyl methacrylate; and

a monomer characterized by formula I:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

R2 is a carbon chain having 1 to 20 carbon atoms or is hydrogen.

The invention also includes a process for the preparation of a film coating composition as described herein which comprises polymerising the dispersions containing ethyl acrylate, methyl methacrylate, and the monomer described herein in the range of 10 to 100°C.

The invention further includes a process to prepare a formulation as described herein which is coated by the above described film coating.

The invention also includes a process to prepare a formulation which includes a plurality of beads with a film coating as described above.

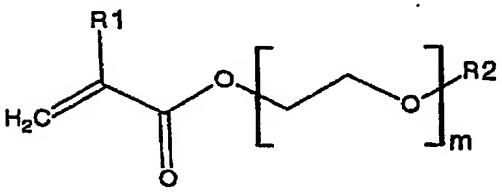
Detailed description of the invention

The invention provides the novel polymer below of:

ethyl acrylate;

methyl methacrylate; and

a monomer characterized by formula I:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

R2 is hydrogen or a carbon chain having 1 to 20 carbon atoms. Moreover, the invention provides a composition including the polymer. Applicants have found that the polymer can serve as a film coat for covering a pharmaceutical core, and that the film coating has good physical properties such that minimal processing problems were experienced. Moreover, the film coating could be reproducibly made having these improved physical properties.

The film coating as described herein requires the addition of no extra additives\excipients. Of course, for different reasons it might be appropriate to add additional additives\excipients to meet special requirements, e.g., during extreme processing and conditions, mixing, etc. Such additives\excipients are known for those skilled in the art and can be but are not limited to:

antiadherents (e g talc and magnesium stearate), binders (e g sucrose, glucose, starch and cellulose), coloring agents (e g titanium dioxide and iron oxide), diluents (e g lactose, mannitol and sorbitol), disintegrants (e g starch derivatives, clays, alginates and gums),

glidants (e g silica and paraffins), lubricants (e g waxes and sodium stearyl fumarate), surfactants (anionics, eg sodium lauryl sulfate; cationics, e g hexyldodecyl ammonium bromide; non-ionic, e g Tween), and polymers (cellulose derivatives, e g hydroxypropyl cellulose; polysaccharides, e g xanthan; other natural polymers like proteins e g albumin; natural rubbers; synthetic polymers, e g poly(meth)acrylates, polyamides, polyanhydrides, polyvinylalcohol, polyvinylacetate, PEO-PPO block-co-polymers, polyvinylpyrrolidone). The use of these materials are described in, e g, H A Lieberman, L Lachman (Eds): Pharmaceutical Dosage Forms: Tablets Volume 1 (Marcel Dekker Inc, NY 1980), ME Aulton (Ed): Pharmaceutics, The science of dosage form design (Churchill Livingstone 1988), and AH Kibbe (Ed): Handbook of Pharmaceutical Excipients (American Pharmaceutical Association, Washington DC and Pharmaceutical Press, London, 2000). The amounts of such additives\excipients depend on the specific purpose as described in these references.

Suitably the film coat has a thickness in the range of 1 to 100 micrometers, preferably in the range of 5 to 50 micrometers and more preferably in the range of 10 to 30 micrometers.

The film coating described herein can be used to coat a pharmaceutical core which includes one or more pharmacologically active ingredients, and optionally one or more pharmaceutically acceptable additives or excipients. The pharmacologically active ingredient can be provided in a plurality of beads and coated with a film coat as defined above. Such film coated beads may be provided in sachets or formulated as a capsule, for example a hard gelatin capsule, or compressed to form tablets using known methods with the optional addition of other pharmaceutically acceptable additives. Coated beads to be compressed into a tablet are obtained by conventional techniques known to those skilled in the art. Also, during this process suitable agents can be added. For example, during the tabletting step suitable fillers, e.g., microcrystalline cellulose, talc, sodium stearyl fumarate etc. can be utilised to give acceptable compression characteristics of the formulation, e.g., hardness of the tablet.

Suitably the beads have a diameter in the range of 0.01-2mm, preferably in the range of 0.05-1.0mm and more preferably in the range of 0.1-0.7mm.

Optionally the beads may contain an insoluble core onto which the active ingredient has been deposited for example by spraying. Suitable materials for the inert core are silicon dioxide, glass or plastic resin particles. Suitable types of plastic material are pharmaceutically acceptable plastics such as polypropylene or polyethylene preferably polypropylene. Such insoluble cores have a size diameter in the range of 0.01-2mm, preferably in the range of 0.05-0.5mm and more preferably in the range of 0.1-0.3mm.

The present invention also includes a controlled-release formulation wherein the pharmacologically active ingredient is controlled over a long period of time, for example longer than 3 hours, e.g., up to 24 hours, in comparison to an immediate release tablet. Preferably the pharmacologically active ingredient has activity in the treatment of cardiovascular or gastrointestinal diseases.

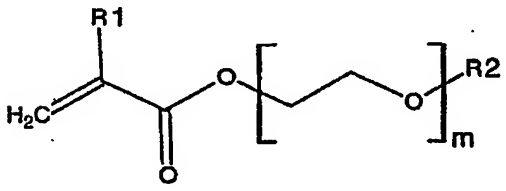
In a preferred embodiment, the invention provides a controlled release metoprolol formulation where a metoprolol core comprising metoprolol or a pharmaceutically acceptable salt thereof and optionally one or more pharmaceutically acceptable excipients or additives, is coated with a film coating described herein. The core including metoprolol or a pharmaceutically acceptable salt thereof can be a plurality of beads which comprise metoprolol or a pharmaceutically acceptable salt thereof. Preferably the beads have an inert core as described previously.

Suitable pharmaceutically acceptable salts of metoprolol include the tartrate, succinate, fumarate or benzoate salts and especially the succinate salt. The S-enantiomer of metoprolol or a salt thereof, particularly the benzoate salt or the sorbate salt, may also be used.

The polymers as described herein for use in a film coating can include a blend or copolymer comprising three or more monomers, e.g., acrylic acid and esters thereof particularly the methyl, ethyl, propyl and butyl esters; and methacrylic acid and esters thereof particularly the methyl, ethyl, propyl and butyl esters, which is dispersed in a substantially aqueous liquid preferably water. Also hydroxylated acrylic and methacrylic esters are included such as the hydroxyethyl methacrylate. Polyethylene glycol acrylates and methacrylates are also included, such as methoxy polyethylene glycol methacrylate, hydroxy polyethylene glycol acrylate, methoxy polyethylene glycol acrylate and hydroxy polyethylene glycol methacrylate. Also alkyl polyethylene glycol acrylates and methacrylates, such as alkyl methoxy polyethylene glycol methacrylate, alkyl hydroxy polyethylene glycol acrylate, alkyl methoxy polyethylene glycol acrylate and alkyl hydroxy polyethylene glycol methacrylate. Included are also acrylate and methacrylate esters of copolymers of ethylene glycol and propylene glycol or butylene glycol.

To obtain different effects such as suitable release rates, processing improvements, etc, the acrylic polymer dispersion described above can be mixed with other acrylic polymer dispersions, or a mixture of other acrylic polymer dispersions including one or more commercial dispersions. Examples of commercial polymer dispersions include, but are not limited to Kollicoat® SR30D (BASF), Kollicoat® EMM30D (BASF), Eudragit® RL30D (Röhm), Eudragit® RS30D (Röhm), Eudragit® NE30D (Röhm), Aquacoat® ECD (FMC), Surelease® (Colorcon), etc.

Suitably the acrylic polymer includes ethyl acrylates, methyl methacrylates and a compound of formula I:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

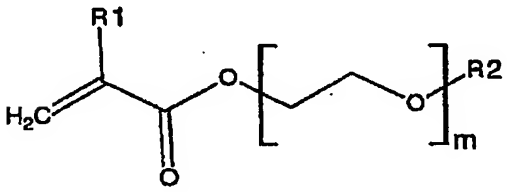
R2 is a carbon chain having 1 to 20 carbon atoms or is hydrogen.

One group of preferred acrylic polymers for this use comprises an ethyl acrylate/ methyl methacrylate/ hydroxyethyl methacrylate copolymer or an ethyl acrylate/ methyl methacrylate/ alkyl polyethoxy acrylate copolymer.

Suitably the amount of ethyl acrylate in the film coating is in the range 8 to 80 % by weight. Preferably the amount of ethyl acrylate in the film coating is in the range 50 to 70 % by weight. More preferably the amount of ethyl acrylate in the film coating is in the range 65 to 70 % by weight.

Suitably the amount of methyl methacrylate in the film coating is in the range 2 to 70 % by weight. Preferably the amount of methyl methacrylate in the film coating is in the range 20 to 40 % by weight. More preferably the amount of methyl methacrylate in the film coating is in the range 30 to 35 % by weight.

Suitably the amount of the compound of formula 1:



(I)

wherein m is an integer from 1-30, R1 is hydrogen or methyl, and R2 is hydrogen or a carbon chain having 1 to 20 carbon atoms, in the film coating is in the range 0.02 to 20 % by weight. In one example, the amount of hydroxyethyl methacrylate in the film coating is in the range 0.5 to 15 % by weight. More preferably the amount of hydroxyethyl methacrylate in the film coating is in the range 1 to 10 % by weight. In another example, the amount of alkyl polyethoxy acrylate in the film coating is in the range 0.02 to 10 % by

weight. Preferably the amount of alkyl polyethoxy acrylate in the film coating is in the range 0.2 to 5 % by weight. More preferably the amount of alkyl polyethoxy acrylate in the film coating is in the range 0.5 to 3 % by weight.

Suitably the water-containing liquid comprises water and a water miscible organic liquid for example lower alkanols e.g. ethanol, propanol or isopropanol. From a safety point of view it is preferred that the proportion of the organic is kept to a minimum but small amounts are tolerable for example in the range of 0 to 20 % by volume. Preferably the liquid is water.

The film-coating composition is particularly suitable for use as an aqueous film-coating composition wherein the film-coat is applied using water as the liquid. This process is particularly advantageous as it negates the need to use environmentally unacceptable organic solvents.

In another aspect the present invention provides processes for the synthesis of suitable acrylic polymers. Therefore there is provided a process for the synthesis of water based acrylic polymer dispersions.

In another aspect the present invention provides processes for the preparation of the film-coating composition. Therefore there is provided a process for the preparation of a film-coating.

In another aspect the present invention provides a process for film coating a pharmaceutical core wherein a film coating composition as defined above is applied to a core. Preferably the film coating composition is applied by spraying for example in a fluidised bed with top spray or bottom spray techniques. Other coating methods used are coating in standard coating pans with perforated pans, Accela-cota, immersion swords, Glatt, or immersion tubes as described in "Theory and Practice in Industrial Pharmacy" edited by Lachman, published by Lea and Feabiger 1986 3rd edition.

In another aspect the invention provides a process to prepare a film coat as defined above comprising removing the liquid from a film coating composition as defined above. Suitably the liquid is removed by evaporation for example by spray drying for example in a fluidised bed. When coating the tablets in a standard coating pan, hot air is used for drying.

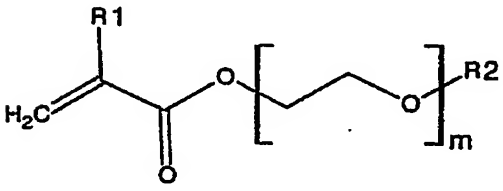
In yet another aspect the invention provides a process to prepare a formulation as defined above comprising coating a pharmaceutical core as defined above with a film coating composition as defined above and optionally containing pharmaceutically acceptable additives as defined above.

In a further aspect the invention provides a process to prepare a formulation in which the pharmacologically active ingredient is provided as a plurality of beads as defined above comprising coating the plurality of beads with a film-coating composition as defined above and optionally containing pharmaceutically acceptable additives or excipients as defined above.

Examples

The following examples are non-limiting and are given by way of illustration only. It will be appreciated by those skilled in the art that the examples are to be looked upon as guidelines, and the invention is not restricted to the exemplified compositions. A wide range of combinations is possible to give film coatings having the necessary properties required for each specific application.

In the examples four different acrylate monomers of formula I were used



(I)

wherein m, R1 and R2 are defined in Table 1 below.

Table 1.

Monomer	m	R1	R2
M1	4	H	C13
M2	10	H	C11
M3	25	H	C18
M4	1	CH_3	H

Example 1: Synthesis of polymer dispersions using M1, M2 and M3.

Polymerisations were carried out using ethyl acrylate, methyl 2-methylacrylate and monomers M1, M2 and M3

The following ingredients were used to prepare dispersions D1, D2 and D3:

D1

Water	677.55 g
Ethyl acrylate	217.75 g
Methyl methacrylate	108.88 g
Monomer M1	2.18 g
Sodium dodecyl sulfate (SDS)	2.18 g
$NaHCO_3$ (0.005 M)	0.27 g
$Na_2S_2O_8$ (initiator)	1.67 g

D2

Water	677.42 g
Ethyl acrylate	218.23 g
Methyl methacrylate	109.12 g
Monomer M2	3.75 g
SDS	2.19 g

$NaHCO_3$ (0.005 M)	0.27 g
$Na_2S_2O_8$	1.72 g

D3

Water	675.31 g
Ethyl acrylate	218.85 g
Methyl methacrylate	109.43 g
Monomer M3	7.15 g
SDS	2.19 g
$NaHCO_3$ (0.005 M)	0.27 g
$Na_2S_2O_8$	1.72 g

The monomers were cleaned from inhibitor by filtering through a column of aluminum oxide. Polymerisations in nitrogen atmosphere were carried out under continous feed conditions at 70 °C in a calorimetric reactor (stirring rate 100 rpm) by first forming a pre-emulsion with SDS in water. The dispersions were purified by dialysis.

Example 2: Synthesis of polymer dispersion using M4.

The following recipe was used to produce dispersion D4:

Water	600 g
Ethyl acrylate	120 g
Methyl methacrylate	70 g
Monomer M4 (hydroxyethyl methacrylate, see Table 1)	10 g
SDS	3 g
Sodium hydroxide (1 M)	2.3 ml
$K_2S_2O_8$ (initiator)	0.6 g

The monomers were distilled to remove the inhibitors. The emulsion polymerisation was carried out in a tightly capped water-jacketed vessel equipped with nitrogen bubbling, and stirred. The monomers, SDS and sodium hydroxide were dispersed in the water and stirred

(50 rpm). The temperature was raised to 50 °C and the initiator was added. The polymerisation was run for 20 hours and the temperature was set to 70 °C for 2 hours. The dispersion was then filtered and cooled.

Example 3: Preparation of films, F1-F4 from examples 1 and 2.

Free films F1-F4 respectively from dispersions D1-D4 were obtained by pouring approximately 10 ml of each dispersion in Teflon moulds. The moulds were then placed in a controlled climate chamber at 25°C and 60% relative humidity for drying and film forming during 19 hours.

Results:

The stickiness of the films was tested by simple manual handling of the films. The films were tested in a permeability experiment, as described in Example 5.

Example 4

Comparative coating: Preparation of films from GMS/PS80/Eudragit NE30D.

Three mixtures of GMS, PS80 and NE30D® were prepared. Different mixing conditions of GMS and PS80 were used to examine the influence of the stirring rate. Thus, first GMS and PS80 were mixed according to either A, B, or C below. Then, appropriate amounts of this dispersion were added to NE30D® to give the intended compositions. The same amounts of GMS, PS80, and NE30D® were used, namely 0.225 g GMS, 0.090 g PS80, and 15.0 g NE30D which gave dispersions with 1.5 %w/w GMS (GMS/particle ratio = 5 %). as describerd in Petereit *et al.* 1995 (*supra*) and Petereit and Weisbrod, (1999) (*supra*):

A: 1 hour; homogenizer at 6000 rpm; 65 °C;

B: 20 min; homogenizer at 3000 rpm; 65 °C;

C: 4 hours; magnet stirring; 65 °C

Free films (10x10 cm^2) of the three dispersions were obtained by pouring approximately 10 ml of each dispersion in Teflon moulds, which were set aside at 25 °C, 60% relative humidity for drying and film-formation during 18 hrs.

Example 5: Permeability of free films.

Pieces of the films F1, F4, A, B, and C prepared according to Examples 1-4 were mounted in diffusion chambers consisting of two chambers separated by a free film (Hjärtstam, *Thesis*, Chalmers University of Technology, Göteborg 1998). The transport of labelled water was followed from the donor side to the receiver side over the membrane at 25 ^{0}C. Appropriate volumes (typically 0.5 mL) were taken from the receiver side at different times. The permeability (m^2 s^{-1} $x10^{12}$) of a film was calculated from the amount of labelled water passing through the membrane in time

Results:

The results from the permeability experiments are shown in Table 2. The results clearly show that the films F1 to F4 show an unexpected low permeability compared to the known films A, B, and C. It is seen that highly variable permeability was obtained with the three GMS/PS80/NE30D dispersions. However, the trend in the data suggested that a protocol which produced better dispersed GMS particles gave a lower permeability (A better than B better than C). Nevertheless, it was not possible to obtain the low permeability shown by films F1 and F4 obtained from the dispersions D1 and D4 according to this invention. Moreover, the permeability of films F1 and F4 were comparable to what could be expected with a free film typical for the organic solvent based film (O) used for coating of the drug metoprolol (Lindstedt, Ragnarsson, and Hjärtstam, *Int J Pharmaceutics* 56, 261 (1989). Thus, superior quality of free film could be obtained with the present invention with no additives and with no processing before film-preparation.

Table 2: Permeability of free films

Film	F1	F4	A	B	C	O
Permeability (m^2 s^{-1} $x10^{12}$)	1.4	3.1	30.1	40.5	51.0	>1.8 (1.8-10)

Example 6: Preparation of coated metoprolol succinate pellets.

Metoprolol succinate beads (size fraction 0.40-0.63 mm) were coated with film dispersion D4. The dispersion was sprayed onto the beads in a laboratory-scale, fluidbed topspray apparatus. The coating conditions were as follows:

Bed weight	500 g
Coating solution	300 g
Spraying rate	6-9 g/min
Atomising air pressure	2 bar
Fluidising air flow rate	30 m^3/h
Inlet air temp.	43 °C
Outlet air temp.	23 °C

Results: No sticking of pellets occured during the process.

Example 7: Release of metoprolol succinate from coated pellets.

The release of metoprolol from about 150 mg pellets according to Example 6 was evaluated in a USP dissolution apparatus No.2 (rotating paddle, 100 rpm). The test medium was 500 ml of phosphate buffer with a pH of 6.8 and ionic strength equal to 0.1 M. The temperature of the bath was set to 37°C. Samples were withdrawn for analysis (absorbance of metoprolol at 274 nm in a 1 cm cell). Amounts of released metoprolol were determined from measurements of the absorbance of a standard metoprolol solution based on the same medium as used in the release experiments.

Results

Table 3. Fraction released from pellets

Time/hrs	1	2	4	6	8	10	12	16	20
(F4) % released	6.6	12.2	22.1	30	37.8	45.3	52.2	65.6	78.1

The results in Table 3 show that a close to constant release profile with modified release properties up to 20 hrs can be achieved.

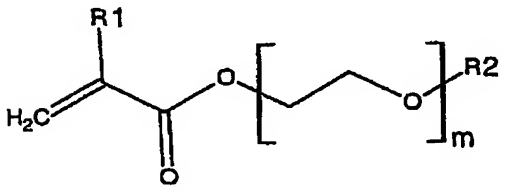
Claims

1. A polymer comprising the following monomers:

ethyl acrylate;

methyl methacrylate; and

a monomer characterized by formula I:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

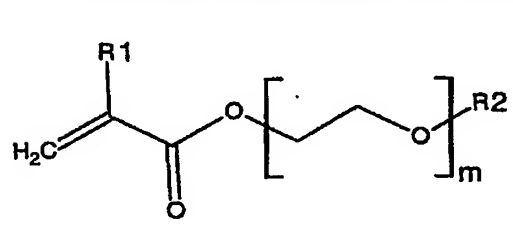
R2 is hydrogen or a carbon chain having 1 to 20 carbon atoms.

2. A composition comprising a polymer of the following monomers:

ethyl acrylate;

methyl methacrylate; and

a monomer characterized by formula I:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

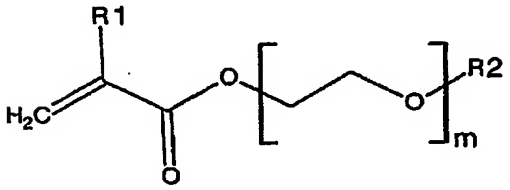
R2 is hydrogen or a carbon chain having 1 to 20 carbon atoms.

3. A film coating for use in coating pharmaceutical formulations comprising a dispersion which comprises a polymer of the following monomers:

ethyl acrylate;

methyl methacrylate; and

a monomer characterized by formula 1:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

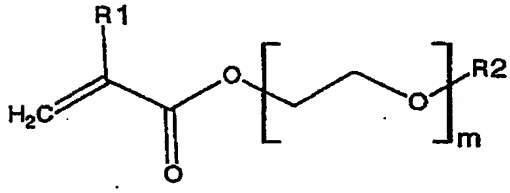
R2 is hydrogen or a carbon chain having 1 to 20 carbon atoms.

4. A film coat covering a pharmaceutical core wherein the core comprises a pharmacologically active ingredient and the film coat comprises a polymer of the following monomers:

an ethyl acrylate;

methyl methacrylate; and

a monomer characterized by formula I:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

R2 is hydrogen or a carbon chain having 1 to 20 carbon atoms.

5. The film coat of claim 4 wherein the pharmacologically active ingredient is a beta-blocking adrenergic agent.

6. The film coat of claim 5 in which the pharmacologically active ingredient is metoprolol or a pharmaceutically acceptable salt thereof.

7. The film coat of claim 6 in which the metoprolol salt is the tartrate, succinate, fumarate or benzoate salt .

8. A pharmaceutical formulation comprising:

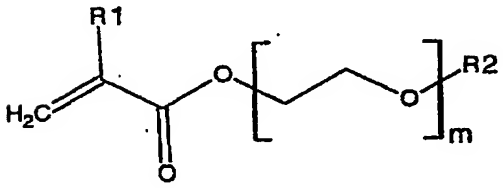
a) a pharmaceutical core comprising a pharmacologically active ingredient; and

b) a film coat comprising a polymer of the following monomers:

(i) ethyl acrylate;

(ii) methyl methacrylate; and,

(iii) a monomer of fomula I:



(I)

wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

R2 is a carbon chain having 1 to 20 carbon atoms or is hydrogen.

9. A pharmaceutical formulation comprising a pharmacologically active ingredient which is provided in a plurality of beads wherein each of the beads is coated with a film coat as defined in claims 3-7.

10. A formulation according to to any one claims 8-9 wherein the formulation is a controlled release formulation.

11. A formulation according to any one of claims 8-10 wherein the pharmacologically active ingredient has activity in the treatment of cardiovascular or gastrointestinal diseases.

12. A formulation according to to any one claim 8-11 in which the pharmacologically active ingredient is a beta-blocking adrenergic agent.

13. A formulation according to claim 12 in which the pharmacologically active ingredient is metoprolol or a pharmaceutically acceptable salt thereof.

14. A formulation according to claim 13 in which the metoprolol salt is the tartrate, succinate, fumarate or benzoate salt .

15. A polymer according to claim 1, a composition according to claim 2, a film coating according to claims 3 or 4, a pharmaceutical formulation according to claim 8 wherein the monomer of formula I is defined as m is 4, R1 is hydrogen and R2 has 13 carbon atoms.

16. A polymer according to claim 1, a composition according to claim 2, a film coating according to claims 3 or 4, or a pharmaceutical formulation according to claim 8, wherein the monomer of formula I is defined as m is 10, R1 is hydrogen and R2 has 11 carbon atoms.

17. A polymer according to claim 1, a composition according to claim 2, a film coating according to claims 3 or 4, or a pharmaceutical formulation according to claim 8 wherein the monomer of formula I is defined as m is 25, R1 is hydrogen and R2 has 18 carbon atoms.

18. A polymer according to claim 1, a composition according to claim 2, a film coating according to claims 3 or 4, or a pharmaceutical formulation according to claim 8 wherein the monomer of formula I is defined as m is 1, R1 is methyl and R2 is hydrogen.

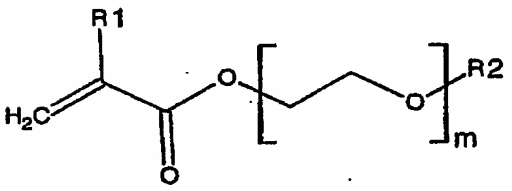
19. A process for the preparation of a polymer comprising polymerizing

an ethyl acrylate;

methyl methacrylate; and

a monomer characterized by formula I:

(I)



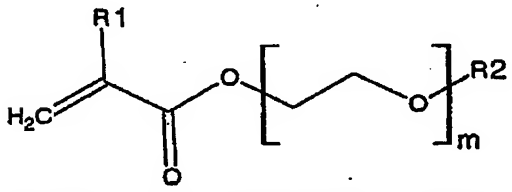
wherein m is an integer from 1-30,

R1 is hydrogen or methyl, and

R2 is a carbon chain having 1 to 20 carbon atoms or is hydrogen.

20. A process for the preparation of a film coating composition according to claim 3 or claim 4 comprising polymerising the dispersions containing ethyl acrylate, methyl methacrylate, and the monomer of formula I:

(I)



wherein m is an integer from 1-30, R1 is hydrogen or methyl, and R2 is a carbon chain having 1 to 20 carbon atoms or is hydrogen, in the range of 10 to 100°C.

21. A process to prepare a formulation as claimed in claim 8 comprising coating the pharmaceutical core with a film coating composition as defined in claims 3 or 4.

22. A process to prepare a formulation as claimed in claim 8 comprising coating a plurality of beads with a film coating composition as defined in claims 3 or 4.

Abstract

The present invention provides a novel film coating.